

assertion would be considered credible by a person of ordinary skill in the art", a rejection should not be imposed for lack of utility.

The claims are directed to a method of tag-directed synthesis of a plurality of compounds. The Examiner is directed to page 17, line 14 – page 18, line 11 of the specification, wherein a number of utilities for the claimed invention may be found:

"An entire compound library or individual library members produced by the methods of the present invention may be evaluated for one or more desired activities in screening assays capable of distinguishing compounds which modulate an activity or possess a desired structural or functional property.

Exemplary assays and functional analyses include, but are not limited to, enzymatic assays, non-enzymatic catalytic assays, protein-protein binding assays, receptor/ligand binding assays and cell-based assays. More specifically, exemplary cell-based methods provided by the present invention are based on; (1) differential binding of library compounds to a cell surface (i.e. binding to cancer cell and not a non-cancer cell), (2) binding of library compounds to components of a cell extract (e.g., binding to a cell fraction produced by separating an entire cell extract on a sucrose gradient), (3) library compounds capable of endocytosis by a cell, and (4) in vivo localization and binding properties of library compounds by injecting the library into an animal. (See, e.g., Arap, W., et al., Science 279(5349): 377-80 (1998) which describes in vivo selection of phage display libraries to isolate peptides that home specifically to tumor blood vessels).

As will be appreciated by those of skill in the art, such assays may be performed on entire libraries of compounds synthesized by the methods described herein or subpopulations derived therefrom.

The number of possible receptor molecules for which ligands may be synthesized and identified by the methods of the present invention is virtually unlimited. Exemplary receptor molecules include, but are not limited to antibodies, growth factors, hormones, enzyme substrates, interferons, interleukins, intracellular and intercellular messengers, lectins, cellular adhesion molecules, and the like. Additional exemplary ligands include, but are not limited to, carbohydrates, non-protein organic compounds, metals, peptide mimetics, non-ribosomally produced polypeptides, conotoxins and polyketides, etc.

Desired compounds produced by the nucleic acid tag-directed combinatorial library methods of the present invention include, but are not limited to, small organic molecules, polyketides, subunit oligomers and catalysts for the synthesis of complex

molecules from simple substrates, e.g., transition metal mediated reactions termed "domino" reactions which are highly efficient processes that allow for production of large libraries of complex structures in relatively few steps beginning with simple precursors. (See, e.g., Tietze and Lieb, *Curr Opin Chem Biol* 2:63-371 (1998))."

Thus, Applicants have asserted a number of specific utilities for the claimed invention. According to M.P.E.P. 608.01(p), "if the asserted utility of a compound is believable on its face to persons skilled in the art in view of the contemporary knowledge in the art, then the burden is on the Examiner to give adequate support for rejections for lack of utility under this section".

The Examiner states that, "Research tools (such as gas chromatographs, screening assays, etc) are useful in the sense that they can be used in conjunction with other method steps to evaluate materials other than themselves or to arrive at some result." Likewise, the claimed method may be used in conjunction with other method steps, such as screening assays (see, page 17, lines 15-18 of the specification) capable of distinguishing compounds which modulate an activity or possess a desired structural or functional property.

Because the claimed invention is supported by several specific asserted utilities, one skilled in the art would clearly know how to use the claimed invention.

In view of the foregoing, Applicants submit that the claims comply with the requirements of 35 U.S.C. §§101 and 112, first paragraph.

II. Rejection Under 35 U.S.C. §112, first paragraph

Claims 1-10 were rejected under 35 U.S.C. §112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention without undue experimentation. This rejection is traversed in view of the following.

The purpose of the enablement provision is to assure that the inventor provides sufficient information about the claimed invention to allow a person of skill in the field of the invention to make and use it without undue experimentation, relying on the patent specification and the knowledge in the art. *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 18 USPQ2d 1001 1006 (Fed. Cir. 1991). As stated in M.P.E.P. §2164.01, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *M.I.T. v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1987).

With respect to how to make the compositions of the invention, the specification provides a number of examples. See, for example, the synthesis of polypeptides and peptide libraries

(page 11, lines 13-17; page 15, line 27 – page 16, line 18), RNA (page 11, line 19), and “small organic molecules, polyketides, subunit oligomers and catalysts for the synthesis of complex molecules from simple substrates, e.g., transition metal mediated reactions termed ‘domino’ reactions which are highly efficient processes that allow for production of large libraries of complex structures in relatively few steps beginning with simple precursors (page 18, lines 6 – 11; also referencing Titze and Lieb, *Curr Opin Chem Biol* 2:63-371 (1998)). Furthermore, as observed by the Examiner on page 7 of Paper No. 8 when referring to the compounds of the instant invention as claims, “...the state of the prior art ... is replete with numerous types of compounds synthesized and or utilized in combinatorial solid and liquid phase chemistry.” Thus, the tag-directed synthesis of a number of compounds are described in the specification and the prior art is replete with numerous examples. Only routine experimentation is required.

As regards the nature of the invention, Applicants have discovered a new method for iterative synthesis of a plurality of compounds wherein a nucleic acid tag directs and encodes the synthesis of the compound to which it is covalently attached. One skilled in the art would understand this method to be a process that will work with a wide variety of compounds synthesized and/or utilized in combinatorial chemistry. As regards the state of the prior art, the Examiner acknowledged that both solid and liquid phase combinatorial chemistry methods were well known. Thus, a great deal was known about synthesizing compounds in a combinatorial manner. The Examiner will also agree that the relative skill of those in the art is quite high.

The breadth of the claims also supports a finding of enablement. The claims require the synthesis of a plurality of compounds utilizing nucleic acid tags that have hybridization sequences and chemical reaction sites, each of which have been defined appropriately.

The Examiner has not provided sufficient evidence or reasoning, as required in *In re Marzocchi and Horton* (CCPA 1971; 439 F2d 220, 169 USPQ 367), to doubt that the full scope of the claims could not be carried out without undue experimentation. The Examiner’s position is that combinatorial library synthesis would be unpredictable. Specifically, the Examiner states that methods involving oligonucleotides to direct the synthesis of combinatorial libraries would be more unpredictable than methods not involving oligonucleotide tag-directed synthesis. However, in the preceding sentence, the Examiner states that the level of predictability is at its highest for oligonucleotide chemistry. “[I]t is incumbent upon Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts truth or accuracy of statement in supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with contested statement; otherwise, there would be no need for applicant to support his presumptively

accurate disclosure." *In re Marzocchi and Horton*, supra. Applicants fail to see how methods involving oligonucleotides, which have the highest level of chemical predictability, to direct synthesis would be more unpredictable than methods not involving oligonucleotide tag-directed synthesis. Nowhere does Terret, or any other reference that the Examiner has provided or that Applicants are aware of, suggest such a conclusion. No evidence or reasoning consistent with the Examiner's position has been presented.

The Office Action further implies, relying on Terret, N.K., that the claims would encompass inoperative embodiments because of the range of predictability for particular compounds synthesized according to the method of the invention. However, case law provides that the "presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art." (*Atlas Powder Co. V. E.I. duPont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414, Fed. Cir. 1984).

Taken in conjunction, a consideration of these factors, and a lack of sufficient evidence or reasoning to the contrary, supports a finding of enablement. Applicants submit that even though a large number of possible compounds are encompassed by the claims, this factor is not determinative. The standard for §112 enablement is that one skilled in the art would be able to use the description of the invention to make and use the claimed invention without undue experimentation. Complex experimentation does not make it undue, if the art typically engages in such experimentation. See *M.I.T.*, supra. As stated above, the techniques for experimental synthesis of compounds in combinatorial chemistry are well known in the art. Accordingly, Applicants submit that the specification fully enables one skilled in the art to make and use the present invention without undue experimentation, thereby satisfying the requirements of 35 U.S.C. §112, first paragraph.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

III. Rejection Under 35 U.S.C. §112, second paragraph

Claims 1-5 and 8-10 were rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. This rejection is traversed in view of the following.

A. "nucleic acid tags"

In claim 1, the term "nucleic acid tags" has been rejected as not providing one of ordinary skill in the art a mean of determining the metes and bounds of the claimed method. The Examiner asserts that it is not clear if the term encompasses an additional, unrecited term that has been described in the specification -- "oligonucleotide analogs". However, the definiteness of claim language is measured solely on the basis of the elements recited in the claim and not in view of additional unrecited features described in the specification. *In re Fisher*, 427 F.2d 833, 166 USPQ 18, 23 (C.C.P.A. 1970), cert. denied, 401 U.S. 956 (1971). Thus, the Examiner has failed to establish a *prima facie* case of indefiniteness.

B. "chemical reaction site"

In claims 1 and 9, the term "chemical reaction site" has been rejected as not providing one of ordinary skill in the art a means of determining the metes and bounds of the claimed invention. The Examiner asserts that the term is indefinite because the specification defines the term as a chemical component capable of forming a variety of chemical bonds, and that any "component" of any compound is 'capable of forming a variety of chemical bonds.'"

The Examiner's rejection parallels the rejection made in *In re Wakefield* (422 F.2d 897, 164 USPQ 636 (C.C.P.A. 1970)). In *Wakefield*, the invention related to a method of making a synthetic polyisoprene having a specific molecular structure. The Examiner rejected certain claims that excluded certain characteristics, contending that the claims would encompass "a virtually unlimited number of materials." *Id.*, 164 USPQ at 641. The CCPA reversed, stating that "[t]he scope of the claim is still definite ... because each recited limitation is definite." *Id.* Similarly, the Examiner in the instant case has rejected the term "chemical reaction site" as being too broad and encompassing any compound capable of forming a variety of chemical bonds. As stated by the CCPA, "[a]n applicant is entitled to claims as broad as the prior art and his disclosure will allow." *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323, 326 (C.C.P.A. 1981). The breadth of a claim is not to be equated with indefiniteness. *In re Miller*, 441 F.2d 689, 169 USPQ 597, 600 (C.C.P.A. 1971). Thus, the Examiner may not reject claims 1 and 9 as indefinite merely because they are broad.

C. "reagent-specific compound intermediate"

In claim 1, the term "reagent-specific compound intermediate" has been rejected, but no basis for the rejection has been provided.

An Examiner must clearly define the problem and why it is a problem in connection with the issue of claim definiteness in order to provide an applicant or any reviewing authority with the information necessary to evaluate the Examiner's position fairly. Applicants submit that the rejection fails to establish a *prima facie* case of indefiniteness. The MPEP provides the following: "The examiner's focus during examination of claims for compliance with the requirement for definiteness ... is whether the claim meets the threshold requirements of clarity and precision, not whether more suitable language or modes of expression are available." *MPEP* §2173.02. The Examiner must clearly and fully state the grounds of the rejection. Absent specific rejections and explanations of indefiniteness, Applicants fail to see where the claim lacks clarity or definiteness.

D. The Examiner has rejected claim 1 as lacking clarity, asserting that a portion of the claim may be read as one of three alternatives -- two of which appear to be identical. Applicants request clarification of the rejection.

E. "oligonucleotide analog"

The Examiner has rejected this term in claim 2 as not providing a means for determining the metes and bounds of the claim. The Examiner has misread and misquoted the specification's guidance regarding this term. The Examiner claims that base-pairing can be considered a physical, rather than biological property; and that the term "oligonucleotide analog" is defined as having only biological activities. However, the term "oligonucleotide analog", as defined on page 8, lines 20-23 of the specification to mean "a nucleic acid that has been modified and which is capable of some or all of the chemical or biological activities of the oligonucleotide from which it was derived." Thus, contrary to the Examiner's assertion, the term encompasses biological and chemical activities.

F. "subunit oligomers"

In claim 3, the phrase "for use in forming a plurality of oligomers with different subunit sequences" has been rejected as being too broad, because, the Examiner asserts, "it is clear that nucleic acids and peptides are encompassed by the claim, but [it] is not possible to determine what other types of molecules are included or excluded from the scope of the claim."

As discussed above, and as stated by the CCPA, "[a]n applicant is entitled to claims as broad as the prior art and his disclosure will allow." *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323, 326 (C.C.P.A. 1981). The breadth of a claim is not to be equated with indefiniteness. *In re*

Miller, 441 F.2d 689, 169 USPQ 597, 600 (C.C.P.A. 1971). Thus, the Examiner may not reject claim 3 as indefinite merely because it is broad.

G. "small molecules"

In claim 4, the term "small molecules" has been rejected as not being clear with regard to the metes and bounds of the claim. Again, the Examiner appears to be rejecting the claim as being indefinite because it is broad. However, as explained above, the Examiner may not reject a claim merely because it is broad.

H. "chemical sequences"

In claim 4, the term "chemical sequence" has been rejected by the Examiner as being "difficult to interpret." However, as the Examiner has observed, the specification provides a definition of the term. It is a fundamental principle under Section 112, second paragraph, that inventors may act as their own lexicographers. *Lear Siegler, Inc. v. Aeroquip Corp.*, 733 F.2d 881, 221 USPQ 1025, 1031 (Fed. Cir. 1984); *Fromson v. Advance Offset Plate, Inc.*, 7210 F.2d 1565, 1549, 219 USPQ 1137, 1140 (Fed. Cir. 1983). Inventors may generally define claim terminology in whatever terms they consider suitable. Furthermore, in determining the meaning of patent claims, words or phrases in a claim will be given their ordinary meaning unless the specification indicates that the inventor used these words or phrases differently. *Jonsson v. Stanley Works*, 903 F.2d 812, 14 USPQ 2d 1863, 1871 (Fed. Cir. 1990) (citing *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 759, 221 USPQ 473, 477 (Fed. Cir. 1984)).

In the instant case, Applicants have properly defined the claim terms such that they are not difficult to interpret.

I. Claims 1 and 5 have been rejected as being incomplete for omitting structural cooperative relationships of elements.

In rejecting a claim under Section 112, second paragraph, an Examiner must establish that one of ordinary skill in the pertinent art, when reading the claim in light of the supporting specification, would not have been able to ascertain with a reasonable degree of precision and particularity the specific area set out and circumscribed by the claim. *Ex parte Wu*, 10 USPQ 2d 2031, 2033 (B.P.A.I. 1989); *In re Moore*, 439 F.2d 1232, 169 USPQ 236, 238 (C.C.P.A. 1971); *In re Hammack*, 427 F.2d 1378, 166 USPQ 204, 208 (C.C.P.A. 1970). In the instant case, the specification provides ample guidance as to the relationships between the elements in the claims.

The Examiner is particularly directed to Fig. 1, which provides a visual representation which may be used to clarify the relationships of the recited claim elements.

It is well settled that the "language of the claims, read in light of the specification" is to be considered when determining whether the claims are definite. *Allen Archery Inc. v. Browning Mfg. Co.*, 819 F.2d 1087, 2 USPQ 2d 1490, 1494 (Fed. Cir. 1987). The definiteness of the language employed must be analyzed not in a vacuum, but in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art. *In re Angstadt*, 537 F.2d 498, 190 USPQ 214, 217 (C.C.P.A. 1976) (quoting *In re Moore*, 439 F.2d 1232, 1235, 169 USPQ 236, 238 (C.C.P.A. 1971)). The law is clear that "if the claims, read in the light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more." *North Am. Vaccine, Inc. v. American Cyanamid Co.*, 7 F.3d 1571, 28 USPQ 2d 1333, 1339 (Fed. Cir. 1993). The drawings may be used in the same way as the written specification to provide evidence relevant to claim interpretation. *Autogiro Co. of Am. v. United States*, 384 F.2d 391, 398, 155 USPQ 697, 703 (Ct. Cl. 1967).

Because the Examiner has not established that the claims are not ascertainable to one of skill in the art in view of the specification, Applicants submit that the rejection is improper.

J. "yield a subpopulation of nucleic acid tags"

Claim 8 has been rejected for not including method steps for the removal of the tags of claim 1.

An Examiner must clearly define the problem and why it is a problem in connection with the issue of claim definiteness in order to provide an applicant or any reviewing authority with the information necessary to evaluate the Examiner's position fairly. Applicants submit that the rejection fails to establish a *prima facie* case of indefiniteness. The MPEP provides the following: "The examiner's focus during examination of claims for compliance with the requirement for definiteness ... is whether the claim meets the threshold requirements of clarity and precision, not whether more suitable language or modes of expression are available." *MPEP* §2173.02. The Examiner must clearly and fully state the grounds of the rejection. Absent specific rejections and explanations of indefiniteness, Applicants fail to see where the claim lacks clarity or definiteness.

In the instant case, no reasoning has been provided as to why the Examiner insists that the compounds must be removed from the tags. Thus, the Examiner has failed to establish a

prima facie case of indefiniteness.

K. "adding a chemical reaction site"

Claims 9 and 10 have been rejected as being incomplete for omitting method steps that provide a means for adding a chemical reaction site.

Applicants submit that there is nothing improper about defining a part of the invention in functional terms. Functional language does not, in and of itself, render a claim improper or indefinite. *In re Swinehart*, 439 F.2d 210, 169 USPQ 226, 229 (C.C.P.A. 1971).

No reasoning has been provided as to why the Examiner insists that there is a gap between steps. Thus, the Examiner has failed to establish a prima facie case of indefiniteness.

Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

IV. Conclusion

In view of the above remarks, the applicants submit that the claims now pending are in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 838-4405.

Respectfully submitted,



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